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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/153,133 09/15/98 LEE

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EXAMINER

PAUL T CLARK  
CLARK & ELBING  
176 FEDERAL STREET  
BOSTON MA 02110

SHARAREH, S

ART UNIT	PAPER NUMBER
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1616

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DATE MAILED:

12/16/99

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

<b>Office Action Summary</b>	Application No. 09/153,133	Applicant(s) Lee et al
	Examiner Shahnam Sharar h	Group Art Unit 1616

Responsive to communication(s) filed on Sep 15, 1998

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle* 1035 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

#### Disposition of Claim

Claim(s) 1-37 is/are pending in the application.

Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

Claim(s) \_\_\_\_\_ is/are allowed.

Claim(s) 1-37 is/are rejected.

Claim(s) \_\_\_\_\_ is/are objected to.

Claims \_\_\_\_\_ are subject to restriction or election requirement.

#### Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

The proposed drawing correction, filed on \_\_\_\_\_ is  approved  disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All  Some\*  None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) \_\_\_\_\_.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

#### Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). 5

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

**--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---**

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## DETAILED ACTION

### ***Priority***

1. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

2. In the instant case, the U.S. application Serial No. 08/729,342 filed October 16, 1996, now pending, the U.S. application Serial No. 08/650,764, filed May 20, 1996, 1993, now pending, and the U.S. application Serial No. 08/416, 182, filed May 19, 1995, now U.S. Patent No. 5,676,976, fail to teach a various adjuvant compositions comprising two adjuvant or adjuvanticity enhancing means such as exogenous or endogenous enhancing means or compositions comprising particles having 0.1-900 nm.

Although some of the broad claims may have support to earlier filed priority applications, the effective priority date used for the examination of the instant invention as a whole (ie, including limitations set forth in dependent claims) is September 15, 1998.

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***Claim Rejections - 35 USC § 102***

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-2, 6-7, 10, 13-14, 28-31, 34, 37 rejected under 35 U.S.C. 102(b) as being anticipated by Towey et al US Patent 2,967,802.

The instant claims are directed to compositions comprising an adjuvant comprising calcium phosphate, and an antigen, wherein said adjuvant is strongly resorbable and said composition is in a form of an injectable paste (gel). The instant claims are also directed to methods of stimulating an immune response in a mammal comprising administering to the mammal said composition.

Towey et al disclose methods of preparing a calcium phosphate preparation by rapidly mixing and stirring a calcium salt with aqueous ammonium phosphate to make a calcium phosphate composition in the form of gel, thus, making a calcium phosphate preparation that inherently possess amorphous characteristics (see col 1 lines 55-71 and col 2 lines 1-20.) Towey further disclose methods of using said composition in the form an adjuvant for formulating an antigen containing composition that can be used to as a vaccine for *Erysipelothrix rhusiopathiae* (see col 3 lines 54-56, col 4 lines 4-9, col 5 lines 24-37.) Therefore, Towey et al meet the limitations set forth in the instant claims.

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5. Claims 1-2, 6, 10-11, 13-16, 19, 23-24, 26-30, 34-35, 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Wilkinson et al US Patent 4,110,432.

The instant claims are directed to compositions comprising an adjuvant comprising calcium phosphate, and an antigen or cytokine, wherein said adjuvant is strongly resorbable and said composition is in a form of an injectable paste. The instant claims are also directed to methods of stimulating an immune response in a mammal comprising administering to the mammal said composition.

Wilkinson et al disclose conjugates of prostaglandin comprising immunogenic a macromolecule selected from mammalian serum (from an endogenous or exogenous source) (see col 2 lines 3-33.), and a suitable adjuvant such as calcium phosphate (see col 6 lines 3-25.) Wilkinson et al further disclose that their composition (including calcium phosphate containing adjuvant) may gradually be prepared with stirring over a period of one hour (which can produce formulations that have crystalline poor characteristics.) Further said composition may be lyophilized to produce amorphous powder (see col 8 lines 10-25.) Wilkinson et al also disclose methods of immunizing mammals (stimulating an immune response) by administering said composition to a mammal (see claims 13 and 21.) Therefore, Wilkinson et al meet the limitations set forth in the instant claims.

6. Claims 1-2, 6, 10-11, 13-16, 19, 23-24, 26-30, 34-35, 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Gupta et al (Vaccine Design Chapter 8 pp 229-248 1995.)

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Gupta et al disclose calcium phosphate compositions that can be used as adjuvant in vaccines (see p. 39.) Gupta specifically disclose that the quality of calcium phosphate products depends on the concentration of the reactants, and the rate at which the reactants are mixed (see p.240.) Gupta also disclose that a slow mixing of such reactants can result in gel formulations with a calcium to phosphorous ratio of 1.35 to 1.55. Further, Gupta et al disclose that calcium phosphate-adsorbed vaccines has successfully been used as an adjuvant for simultaneous immunizations with diphtheria, tetanus, polio, BCG etc.. (see p 241, 3.2.) Finally, Gupta disclose that the potency of vaccine formulations can be increased by incorporation of other adjuvant-active components (see p. 241, last paragraph.) Therefore, Gupta et al meet the limitations set forth in the instant claims.

***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 1-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reyveld US Patent 4,016,252, Gupta et al (Vaccine Design Chapter 8 pp 229-248 1995.), Wilkinson et al US Patent 4,110,432 and Kossovsky et al US Patent 5,462,751.

The instant claims are directed to compositions comprising an adjuvant comprising calcium phosphate, and an antigen or cytokine, wherein said adjuvant is strongly resorbable and

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said composition is in a form of an injectable paste. The instant claims are also directed to methods of stimulating an immune response in a mammal comprising administering to the mammal said composition.

Reyveld teach methods of improving vaccine formulations by using calcium phosphate gel (an amorphous formulation, or a poor crystalline composite) composition as an adjuvant, wherein the calcium to phosphate ratio is from 1.62 to 1.85 (see abstract, col 2 lines 1-15.) Reyveld fails to teach the incorporation of cytokines in his vaccine preparations.

Gupta et al disclose calcium phosphate compositions that can be used as adjuvant in vaccines (see p. 39) Gupta specifically disclose that the quality of calcium phosphate products depends on the concentration of the reactants, and the rate at which the reactants are mixed (see p.240.) Gupta also disclose that a slow mixing of such reactants can result in gel formulations with a calcium to phosphorous ratio of 1.35 to 1.55. Further, Gupta et al disclose that calcium phosphate-adsorbed vaccines has successfully been used as an adjuvant for simultaneous immunizations with diphtheria, tetanus, polio, BCG etc.. (see p 241, 3.2.) Gupta, also teach that the use of a second or third adjuvant in a vaccine preparation. Gupta et al, however, fail to teach the incorporation of cytokines in a vaccine formulation.

Wilkinson et al disclose conjugates of prostaglandin comprising an immunogenic macromolecule comprising various moieties that are selected from a mammalian serum (from an endogenous or exogenous source) (see col 2 lines 3-33.), and a suitable adjuvant such as calcium phosphate (see col 6 lines 3-25.) Wilkinson et al further disclose that their composition (including

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calcium phosphate containing adjuvant) may gradually be prepared with stirring over a period of one hour (which yield to formulations with crystalline poor characteristics.) Further said composition may be lyophilized to produce amorphous powder (see col 8 lines 10-25.)

Wilkinson et al also disclose methods of immunizing mammals (stimulating an immune response) by administering said composition to a mammal (see claims 13 and 21.) Wilkinson et al, however fail to indicate the preferred calcium to phosphorus ratio of their amorphous composition or further indicate specific cytokines that can be incorporated in a vaccine formulation.

Kossovsky et al teach nanocrystalline core comprising calcium phosphate moieties in sizes of 5 to 150 nm for use in pharmaceutical compositions. Kossovsky also teach that because of its small particle size their nanoparticle can avoid being removed from circulation by Reticulo-Endothelial System (RES), therefore, their pharmaceutical compositions possessing such properties are effective drug delivery constructs. In addition Kossovsky et al further teach that their nanoparticles can be used in making various pharmaceutical compositions such as vaccines when combined with suitable adjuvant (see col 3 and 4.) Kossovsky et al do not teach the specific methods of stimulating an immunogenic response in a mammal.

Examiner takes the position that peptides encompassing those that can cause a biological activity (including various cytokines eg. IL-1, IL-2, IL-3, etc.) can be employed in a manner known in the art to stimulate an immune response of a host subject by acting as a vaccine in combination with an adjuvant (as taught by Wilkinson).

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Reyveld, Gupta, Wilkinson, and Kossovsky all teach various methods of stimulating an immune response in a host subject, therefore, they are viewed as being in the same field of endeavor.

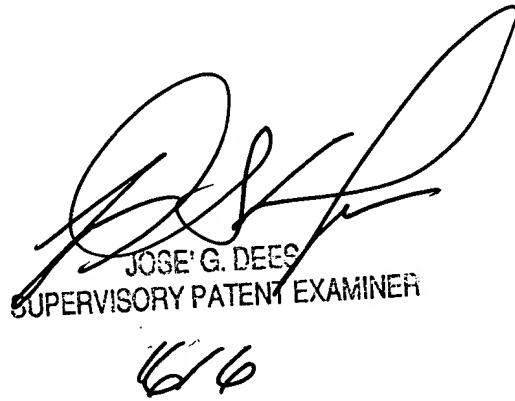
It has been established that the prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success, therefore, although Reyveld does not disclose methods of preparing a vaccine comprising at least two adjuvant and a cytokine, one skilled in the art would have been motivated to combine various known components taught by Gupta, Wilkinson, and Kossovsky and formulate compositions for stimulating an immune in a mammal that comprise calcium phosphate adjuvants; as taught by Gupta, large macromolecules such as lymphokines and cytokines; as taught by Wilkinson and Kossovsky, and smaller size particles that are not filtered by RES; as taught by Kossovsky, because said skilled artisan would have had a reasonable expectation to succeed in formulating a preparation that stimulates the immune response for a longer period time. In addition, since expected beneficial results are evidence of obviousness of a claimed invention, formulating compositions with one or two adjuvant would not make the claimed invention patentable over the prior art if the criticality for additional adjuvant is not demonstrated. Therefore, it would have been obvious to one skilled artisan to create immune response inducing adjuvant compositions comprising combinations of adjuvant moieties, because prior art teachings indicate an enhanced potency in prophylactic medicine when such combinations have been used.

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*Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh, PharmD whose telephone number is (703) 306-5400. The examiner can normally be reached on Monday to Friday from 8:30 a.m. to 5:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Jose Dees can be reached on 703-308-4628. The fax phone number for this Group is 703-308-4556. Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is 703-308-1235.

*sjs 12/8/99*



JOSE G. DEES  
SUPERVISORY PATENT EXAMINER  
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